RADIATION RESEARCH 125, 214-222 (1991)

Frequent Chest X-Ray Fluoroscopy and Breast Cancer Incidence among Tuberculosis Patients in Massachusetts

JOHN D. BOICE, JR.,* DALE PRESTON,*† FAITH G. DAVIS,‡ AND RICHARD R. MONSON§

Radiation Epidemiology Branch. Executive Plaza North, Suite 408. National Cancer lnstitute, National Institutes of Health, Bethesda, Maryland 20892; †Department of Statistics, Radiation Effects Research Foundation. Hiroshima, Japan; ‡Epidemiology and Biostatistics Program, School of Public Health, University of Illinois at Chicago. Chicago, Illinois; and §Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, Massachusetts 02115

BOICE, J. D., JR., PRESTON, D., DAVIS, F. G., AND MONSON, R. R. Frequent Chest X-Ray Fluoroscope and Breast Cancer Incidence among Tuberculosis Patients in Massachusetts. *Radiat. Res.* 125,214-222 (1991).

The incidence of breast cancer was determined in 4940 women treated for tuberculosis between 1925 and 1954 in Massachusetts. Among 2573 women examined by X-ray fluoroscopy an average of 88 times during lung collapse therapy and followed for an average of 30 years, 147 breast cancers occurred in contrast to 113.6 expected [observed/expected (O/E) = 1.29; 95% confidence interval (CI) = 1.1 - 1.5]. No excess of breast cancer was seen among 2367 women treated by other means: 87 observed versus 100.9 expected. Increased rates for breast cancer were not apparent until about 10 to 15 years after the initial fluoroscopy examination. Excess risk then remained high throughout all intervals of follow-up, up to 50 years after first exposure. Age at exposure strongly influenced the risk of radiation-induced breast cancer with young women being at highest risk and those over age 40 being at lowest risk [relative risk (RR) = 1.06]. Mean radiation dose to the breast was estimated to be 79 cGy, and there was strong evidence for a linear relationship between dose and breast cancer risk. Allowing for a 10-year minimum latent period, the relative risk at 1 Gy was estimated as 1.61 and the absolute excess as 10.7 per 10^4 woman-years per gray. When compared to other studies. our data suggest that the breast is one of the most sensitive tissues to the carcinogenic force of radiation, that fractionated exposures are similar to single exposures of the same total dose in their ability to induce breast cancer, that risk remains high for many years after exposure, and that young women are especially vulnerable to radiation injury.

INTRODUCTION

The screening of asymptomatic women by X-ray mammography and physical examination has been recommended strongly as a means to reduce breast cancer mortality *(1-3).* Concerns have been raised, however, over the possible hazard from frequent exposure to low-dose radiation *(4-7).* Important questions remain about the dose-response relationship at low levels, the modifying effect that age at exposure has on risk, and the length of time over which the increased risk is expressed. One population that may be relevant to these issues is women with tuberculosis (TB) who underwent repeated fluoroscopic X-ray examinations during lung collapse therapy. Such women were often examined several times a month for 3 to 5 years and received considerable radiation exposure to their breasts. In this paper we combine the results from an extended follow-up of TB patients treated by pneumothorax in Massachusetts (8, 9) with the findings from two new groups of TB patients never before evaluated for breast cancer incidence *(10, 11).*

METHODS

Study population. Women diagnosed with pulmonary TB between 1925 and 1954 and discharged from 12 Massachusetts hospitals were identified by a review of approximately 30.000 medical records. The exposed group consisted of women who received lung collapse treatment by either pneumothorax or pneumoperitoneum. These procedures involved repeated injections of air into the pleural space or peritoneal cavity for up to 5 or more years. The degree of lung collapse was inspected at the time of each treatment by X-ray fluoroscopy of the chest. A comparison group consisted of all women with tuberculosis who were discharged from the same hospitals but who did not receive lung collapse therapy. These women were treated primarily with bed rest or with surgical procedures that either removed a lobe or all of the lung (lobectomy or pneumonectomy) or caused a permanent collapse (thoracoplasty).

A total of 6719 women were initially selected for study, including 1758 women from an earlier study of TB patients treated at two hospitals in Middlesex County (subcohort 1) *(8, 9)* and 4961 women from two new cohorts treated at 10 other hospitals in Massachusetts (subcohorts 2 and 3) *(10, 11).* Because active tracing of subcohorts 2 and 3 did not begin until 1980, the ascertainment of incident breast cancers occurring shortly after hospital discharge proved difficult. Prior to 1970, for example, 1514 women had died for whom personal contact was not possible and for whom tracing and interviewing relatives was not feasible. To address this problem, only women alive as of December 31, 1969 were included in the analysis of subcohorts 2 and 3. Overall, 1779 women were excluded, including 104 women for whom no follow-up information was available beyond the date of discharge, 41 breast cancers identified from death certificates, and 27 breast cancers identified from questionnaire responses. (Based on population rates, about 90 breast cancers would have been ex-

0033-7587/91 $3.00

TABLE I
Follow-up Status of Women with Tuberculosis as of January 1, 1986, by X-Ray Exposure Classification

Follow-up status	Exposed (%)	Nonexposed (%)	Total (%)
Alive	1421 (55.2)	1424 (60.2)	2845 (57.6)
Dead	937 (36.4)	719 (30.4)	1656 (33.5)
Status uncertain[a]	215 (8.4)	224 (9.4)	439 (8.9)
Total	2573 (100)	2367 (100)	4940 (100)

[a] 81.3% of these women completed a questionnaire prior to 1986. Follow-up information was thus obtained on 98.4% of the study population.

pected among those excluded from analysis.) The final study population consisted of 2573 women who received lung collapse therapy and 2367 women with tuberculosis treated by other means.

Patient follow-up. For subcohort 1 a comprehensive location effort was mounted in 1970 and continued through the present *(12).* The follow-up was extended an additional 6 years beyond that reported previously *(9).* Tracing efforts began in the early 1980s for subcohorts 2 and 3. Follow-up methods involved periodic questionnaire mailings, telephone contacts, city directories and town lists, Departments of Vital Statistics in Massachusetts and other states, state drivers license registries, relatives, credit bureaus, post office address corrections, and the Health Care Financing Administration. Mortality was determined through these sources and also the National Death Index, the Social Security Administration, and the death indices of Massachusetts and several other large states, and death certificates were obtained.

Vital status as of January 1, 1986 was known for 91% of the 4940 patients. Because women in our study are interviewed every 3–5 years, the percentages in Table I reflect in large part the selection of a somewhat arbitrary common closing date. For example, 357 of the 439 subjects with uncertain vital status as of 1986 actually completed a questionnaire prior to 1986. Relatively recent follow-up information thus was missing for only 1.6% of the study population.

A questionnaire was mailed to all women found alive. The last questionnaire contact was in July 1989. Overall, 60% of the study population completed the health questionnaire, 15% were nonrespondents, and 25% had died prior to the start of the various studies. Some 343 women who responded to the questionnaire subsequently died. The response rate for the 3740 women sent the questionnaire, after several mailings and telephone contact, was 80%, The response rate was 80.7%. for the exposed group and 79.5% for the comparison group. Women who did not respond to the questionnaire were assumed to be free of breast cancer for the purposes of this analysis.

Identification of breast cancer. Overall, 307 breast cancer cases were identified from medical records, mail and telephone questionnaire responses, and death certificates. The additional follow-up of subcohort 1 increased the number of breast cancers from 74 to I I 7. SubCohorts 2 and 3 contributed a total of 190 incident breast cancers of which 68 occurred prior to December 31,1969, and were excluded from analyses. Of the 239 breast cancers eligible for analysis, 43% were initially identified from death certificates, 52% from questionnaire responses, and 5% from medical records. Histologic confirmation was obtained on 91.5% of the cases by contacting all hospitals in which a mastectomy or breast cancer diagnosis occurred. A date of mastectomy or breast cancer diagnosis was obtained for all cases, Bilateral breast cancers were diagnosed within 2 months of each other in five women. all but one exposed, and were counted as a single breast cancer *(13).* Ten women, all exposed. developed bilateral breast cancer more than 2 months apart, and both cancers were included in most analyses. One woman had a third primary breast cancer diagnosed after lumpectomy and radiotherapy for her second primary. This third malignancy was not included.

Radiation dose to the breast. Radiation dose absorbed by the breast during X-ray fluoroscopy was estimated using methods described previously, taking into account the number of lung collapse treatments, calendar year of exposure, age at treatment, and exposure settings of the fluoroscopy machines in use during the years when lung collapse was popular *(9, 14).* An adjustment for different breast sizes was made based on age at exposure. The number of lung collapse treatments and associated X-ray fluoroscopy examinations were determined from medical records of ail sanatoria where treatment occurred. Most of the physicians who conducted the examinations (and the patients themselves) were interviewed regarding the fluoroscopic procedures used during the lung-collapse sessions. The patient questionnaire also included items on orientation and rotation during the fluoroscopic examinations. The average absorbed dose to the glandular tissue *in* the breast per Roentgen of entrance skin exposure, free-in-air, was calculated for 26 specific exposure situations. The average fluoroscopic examination was estimated to have lasted 15s, and all patients were estimated, on average, to have faced the X-ray tube 25% of the time. Cumulative absorbed doses ranged from I to 640 cGy (mean, 79 cGy). The cumulative dose from all nonfluoroscopic chest X rays was estimated to be less than 1 cGy and was not considered in any of the dose analyses.

Statistical methods. The risk of radiation-induced breast cancer was estimated by comparing the cumulative incidence of both exposed and nonexposed tuberculosis patients, by contrasting the observed numbers of breast cancers with that expected within the population at large, and by Poisson regression models. Woman-years (WY) of observation were computed from the date of discharge from the index hospitalization (mean, 1942) for subcohort 1 and December 31, 1969, for subcohorts 2 and 3. The end of follow-up was then taken as the date of death for those who died, the date of last questionnaire response for those who responded, the date last known to be alive for nonresponders or those lost to follow-up, or the date of breast cancer diagnosis. Age at first exposure was determined from the date of first treatment by lung collapse, or the date of tuberculosis diagnosis for the nonexposed.

Expected (E) numbers of breast cancers were estimated by multiplying the age- and calendar year-specific WY of observation times the corresponding incidence rates from the population of Connecticut, updated through 1986 *(15,16),* To correspond to the practices of the Connecticut Tumor Registry with regard to registering multiple primary cancers *(13),* second cancers in the contralateral breasts were counted in the observed (0) values if they occurred at least 2 months after the initial breast cancer. Maximum likelihood methods were used to compute an indirectly standardized relative risk (RR), as the ratio of the O/E values for the exposed and nonexposed, adjusted for age, calendar time. and subcohort differences in background rates. Excess risks were derived from this approach used to estimate RR.

Breast cancer incidence rates were also modeled using piecewise-constant hazard function models for data grouped on absorbed dose, age at exposure, attained age, time since exposure, calendar time, and TB subcohort. Parameter estimates for relative and time-dependent excess risk models were computed using maximum-likelihood Poisson regression methods with AM FIT, a program for the analysis of general rate models with grouped survival data *(17, 18).* The modeling was based upon external comparisons with the Connecticut rates.

The relative risk associated with an exposure to dose d was usually modeled as

$$1 + f(d)\exp\{\beta z\},$$

where $f(d)$ was a linear or quadratic function of dose and z a vector of covariates representing possible dose-effect modifiers. The deviance, a

TABLE II
Summary of Breast Cancer Incidence among Tuberculosis Patients by X-Ray Exposure Classification

	Exposed	Nonexposed
No. of Women	2,573	2,367
Breast cancers		
Observed (O)[a]	147	87
Expected (E)[b]	113.6	100.91
O/E	1.29	0.86
Woman-years at risk (WY)	56,965	48,919
Incidence/1,000 WY	2.58	1.78
Mean breast dose (cGy)	79	0

[a] Excludes four simultaneous breast cancers among exposed and one among nonexposed.
[b] Based on age- and calendar-year-specific incidence rates from the state of Connecticut.

measure of unexplained variability, was used to compare alternative models *(19)*. For nested models, the change in the deviance, or likelihood ratio statistic, was evaluated in terms of its asymptotic null distribution as a χ^2 variate with degrees of freedom equal to the difference in the number of estimated parameters between the two models. Whenever feasible, confidence intervals were computed based upon the direct examination of the likelihood as a function of the parameter of interest. These likelihood-based bounds *(20)* provide a more accurate representation of the distribution of a parameter than the commonly used Wald-type bounds ($\beta \pm z_{\alpha/2}\sigma_\beta$).

Unless explicitly stated otherwise, both fitted relative and absolute excess risk estimates were derived from relative risk models. Fitted excess risk estimates were computed by summing the fitted excess cases over the cells in the category of interest and dividing by the corresponding WY and breast dose.

RESULTS

Overall, 105,884 woman-years of observation were accrued. The women had their first fluoroscopic examination some time between 1925 and 1954 (mean 1942); the average age at first fluoroscopy was 26 years. TB was diagnosed among the nonexposed during the period 1925 and 1954 (mean 1942). The average age at discharge from hospital was 27.2 years, and the average time between date of discharge and end of follow-up was 30.4 years. The average period at risk for breast cancer development was 22 years, which is less than the previous interval because follow-up for subcohorts 2 and 3 did not begin until 1970.

Among the 2573 women repeatedly exposed to X-ray fluoroscopy an average of 88 times, 147 breast cancers occurred in contrast to 113.6 expected based on general population rates from Connecticut (O/E = 1.29; 95% CI = 1.1-1.5). The radiation dose to the breast was estimated as 79 cGy. No excess risk was seen among the 2367 women treated by other means: 87 observed and 100.9 expected (Table 11). The O/E ratio for the nonexposed women differed significantly between subcohort 1 and subcohorts 2 and 3, 1.07 vs 0.73, suggesting a difference in background rates of breast cancer. The subcohort differences were taken into account in all subsequent analyses. Radiation risk estimates, however, did not differ significantly by TB subcohort ($P = 0.4$).

Cancer risk increased significantly with increasing radiation dose to the breast (Table III, Fig. 1). Allowing for a 10-year minimum latent period, the relative risk at 1 Gy was estimated as 1.61 (95% CI = 1.30-2.01) and the absolute excess as $10.7/10^4$ WY-Gy (95% CI = 6.0-15.8).

The best-fitting dose–response models were linear in dose and included an age-at-exposure effect (Table IV). A dose-squared model provided an unsatisfactory fit to the observed data, and a linear-quadratic model did not provide a significant improvement in fit over the linear model ($P = 0.5$).

The risk of radiation-induced breast cancer by age at first fluoroscopic X-ray examination is presented in Table V. Risk was significantly high among women examined by fluoroscopy between the ages of 15 and 24, and risk decreased significantly with increasing age at exposure ($P = 0.03$). Women over the age of 40 years when first exposed were at low risk (5 observed versus 5.69 expected).

Excess breast cancers were not apparent until about 15 years after first exposure, and risk then remained high for the period of observation, over 50 years (Table VI). After 15 years, the RRs varied between 1.23 and 1.65, but not significantly. Overall, the data were generally consistent with a constant RR model over time, after a minimum latent period of about 10 years had passed. On an absolute scale, however, the excess risk increased significantly with time.

The final model describing the pattern of risk following radiation exposure was $RR = 1 + 0.708\, de^{\{-0.0744(A-20)\}}$, where A is the age of the woman at exposure and d is the radiation absorbed dose to breast in Gy. Because of the parameterization used, the constant term (0.708) refers to the risk for a woman who was 20 years old at the time of exposure. The estimated RR at 1 Gy for women exposed at age 15, 20, 35, and 45 years are 2.0, 1.7, 1.2, and 1.1, respectively. The model suggests that the excess RR per unit dose decreases by about 7% for each l-year increase in age at exposure. The fitted RR and absolute excess risk estimates presented in Tables III, V, and VI are based on the above model. These values are generally similar to the observed values.

DISCUSSION

Women repeatedly exposed to X-ray fluoroscopy were at a significant increased risk of developing breast cancer later in life. The excess did not appear until about 15 years after exposure and remained high throughout 50 years of observation, Exposures during ages 15-24 years carried the greatest risk. Women exposed over age 40 were at minimal risk.

TABLE III
Observed and Expected Breast Cancer Cases and Woman-Years at Risk by Radiation Absorbed Dose to the Breast

	Radiation dose to breast (cGy)						
	0	1–99	100–199	200–299	300+	Unknown	Total exposed (known dose)
Exposed							
No. of women	2,367	1,675	553	135	64	146	2,427
Woman-years	48,919	33,724	15,453	3757	1675	2356	54,609
Mean absorbed dose, cGy	0	36	136	242	375	—	79
Breast cancer cases							
Observed (O)	87	75	44	14	9	5	142
Expected (E)	100.9	70.6	28.0	6.62	2.44	5.98	107.6
O/E	0.86	1.06	1.57*	2.11*	3.68*	0.84	1.32*
Relative risk[a]	1.00	1.21	1.66*	2.22*	3.83*	1.02	1.44*
Fitted relative risk[b]	1.00	1.18	1.76	2.46	3.60	—	1.48
Excess risk[a] $\times 10^{-4}$ WY	0.00	3.89	11.3*	20.5*	39.7*	0.45	8.00*
Fitted excess risk[b] $\times 10^{-4}$ WY	0.00	3.36	12.9	24.3	36.2	—	8.50

[a] Based on maximum-likelihood methods to compute adjusted risk estimates of the ratio of O/E values between exposed and nonexposed, adjusting for differences in background rates between subcohorts. Excess risk was also derived from this approach.
[b] Based on best-fitting linear dose–response model accounting for age, calendar year, follow-up, and subcohort.
* $P < 0.05$ (one-sided).

A straight line provided the best description of the relationship between radiation dose and risk of breast cancer.

TB patients differ from most other irradiated populations in being exposed to relatively low radiation doses, on the order of 1 cGy, several times a month for up to 5 years *(8, 21, 22)*. Brief, high-dose exposures characterize most epidemiological studies, e.g., atomic bomb survivors *(23)* and women treated with radiotherapy for benign breast conditions *(24, 25)*. Practically all environmental, occupational, and nontherapeutic medical exposures, however, involve radiation doses no greater than those received by TB patients from a single fluoroscopy, yet cumulative exposures following these chest fluoroscopies were high enough to engender measurable excess risks. Thus risk estimates based on these types of exposure situations may be directly relevant to public health concerns.

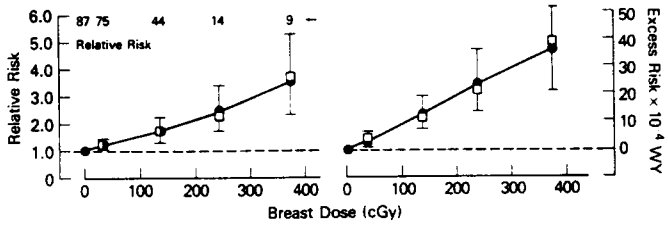

FIG. 1. Relative risk and excess risk of breast cancer by radiation dose to the breast among tuberculosis patients subjected to multiple chest fluoroscopies. (□) Observed data; (●) estimated risks based on the best-fitting dose-response model (linear in dose with a continuous age-at-exposure effect). Ninety-five percent likelihood-based confidence limits about the fitted risks are presented. Numbers to the left of the arrow are the numbers of breast cancers at each point for mean absorbed dose used in the estimates of both the relative and excess risk.

In contrast to animal and cellular experiments which generally indicate that radiation effects are reduced when exposures are spread over time *(26, 27)*, risk estimates from our study are surprisingly similar to those from studies involving high-dose-rate exposures *(28, 29)*. These comparisons suggest that distributing the dose over several years does not appreciably reduce the risk for radiation-induced breast cancer. The breast, however, may be unique in this regard, since the risks of radiogenic lung cancer *(11)* and thyroid cancer *(30, 31)* appear to be much lower when dose is accumulated gradually over time.

While highly fractionated exposures resulted in a substantial increase in breast cancer in our series, no increase in lung cancer was noted, despite organ doses of the order of 1 Gy *(11)*. In one experimental study of female BALB/c mice, the breast was also found to be more vulnerable to the carcinogenic effects of radiation than the lung *(32)*. Further, the carcinogenic response to fractionated exposures appeared to depend not only on the tissue irradiated, but also on the dose per fraction. At a sufficiently low dose per fraction (1 cGy/fraction), the risk of radiogenic breast cancer in the BALB/c mouse was reduced appreciably. In contrast, little effect of higher dose fractionation has been seen in studies of Sprague-Dawley rats *(33)*. Thus, while these experimental results are of considerable theoretical interest, "their quantitative application to humans is problematic" *(34)*.

Because no exposed population has been followed for life, it is not known whether the risk of radiation-induced solid tumors will eventually decrease with time as appears to be the case for radiogenic leukemia (35). Risk for nonleukemia cancer is still increased 30 and more years after expo-

TABLE IV
Evaluation of Various Dose–Response Models

	Model[a]	Parameter	Estimate[b]	95% CI	Deviance[c] difference
Linear	$I = a_{age,\,time}(1 + a_1 D)$	a_1	0.71	(0.40, 1.08)	0.26
Quadratic	$I = a_{age,\,time}(1 + a_2 D^2)$	a_2	0.22	(0.10, 0.41)	6.29
Linear–quadratic	$I = a_{age,\,time}(1 + a_1 D + a_2 D^2)$	a_1	0.85	(0.19, 1.73)	0.00
		a_2	−0.07	(−0.28, 0.21)	

[a] I denotes breast cancer incidence; D denotes breast dose (cGy); $a_{age,\,time}$ denotes background parameter adjusted for age and time. The model also includes a multiplicative age-at-exposure effect on the excess RR (not shown).

[b] Based on these models, the estimated RR for a 20-year-old exposed to 1 Gy are 1.70, 1.22, and 1.81 for the linear, quadratic, and linear–quadratic models, respectively.

[c] The deviance is a measure of unexplained variance used to assess goodness of fit of different nested models. The deviance differences presented are the differences between the indicated model and the linear–quadratic model. This difference can be interpreted as a single degree-of-freedom χ^2 statistic of the adequacy of the simpler method. The results indicate that the linear model describes these data as well as the linear–quadratic ($P > 0.5$), but that the pure quadratic model does not fit well ($P = 0.01$).

sure among atomic bomb survivors (36) and in cervical cancer patients given radiotherapy (37). On the other hand, total cancer risk among British ankylosing spondylitis patients decreased to near normal levels 25 years after radiotherapy to the spine (38). The recent study of Canadian TB patients suggested a drop in relative risk with time (22), but this was based on mortality data, which is not as sensitive an indicator of radiation effects as incidence data and may be influenced by inaccuracies in death certificate diagnoses as well as by improvements in treatment and survival of

TABLE V
Observed and Expected Breast Cancer Cases and Woman-Years at Risk by Age at First Fluoroscopic X-Ray Examination (Exposed) or at First Tuberculosis Diagnosis (Nonexposed)

	Age at First Exposure or TB Diagnosis (yr)						
	0–14	15–19	20–24	25–29	30–39	40+	Total
Exposed							
No. of women[a]	110	474	701	538	465	139	2,427
Woman-years (WY)	3,312	12,152	15,616	11,946	9383	2201	54,609
Mean absorbed dose, cGy	133	98	82	70	64	47	79
Breast cancer cases							
Observed (O)	6	39	47	29	16	5	142
Expected (E)	3.39	18.6	30.7	26.0	23.3	5.69	107.6
O/E	1.77	2.10*	1.53*	1.12	0.69	0.88	1.32*
Nonexposed							
No. of women	486	340	395	394	479	273	2,369
Woman-years	12,652	8,184	7,995	7,746	9000	3342	48,919
Breast cancer cases							
Observed (O)	18	15	20	11	15	8	87
Expected (E)	19.2	12.8	16.1	18.6	23.7	10.5	100.9
O/E	0.94	1.17	1.24	0.59	0.63	0.76	0.86
Relative risk[b]	1.64	2.26*	1.72*	1.24	0.76	0.94	1.44*
Fitted relative risk[c]	2.76	1.90	1.53	1.31	1.16	1.06	1.48
Excess risk[b] $\times 10^{-4}$ WY-Gy	4.85	16.7*	13.5*	5.91	−8.25	−2.60	8.00*
Fitted excess risk[c] $\times 10^{-4}$ WY-Gy	13.85	12.7	11.3	8.60	5.45	2.88	10.7

[a] Number of women contributing WY of observation in these intervals. Variation is due to survival and to the wide range of intervals between exposure and start of follow-up for many individuals. Women with unknown doses excluded.

[b] Based on maximum-likelihood methods to compute adjusted risk estimates of the ratio of O/E values between exposed and nonexposed, adjusting for differences in background rates between subcohorts. Excess risk also derived from this approach.

[c] Based on best-fitting linear dose–response model accounting for age, calendar year, follow-up, and subcohort.

* $P < 0.05$ (one-sided).

TABLE VI
Observed and Expected Breast Cancer Cases and Woman-Years at Risk by Time since First Fluoroscopic X-ray Examination (Exposed) or Time since First Tuberculosis Diagnosis (Nonexposed)

	Time since first exposure (exposed) or TB diagnosis (nonexposed) (yr)							
	0–9	10–14	15–19	20–29	30–39	40–49	50+	Total
Exposed								
No. of women[a]	1020	884	1070	1,677	2,034	1352	355	2,427
Woman-years (WY)	7892	4312	4510	12,726	15,880	8468	821	54,609
Mean absorbed dose, cGy	96	101	87	80	81	93	92	79
Breast cancer cases								
Observed (O)	3	2	6	32	51	43	5	142
Expected (E)	2.22	2.52	4.46	23.09	42.28	29.52	3.53	107.6
O/E	1.35	0.79	1.34	1.39*	1.21	1.46*	1.42	1.32*
Nonexposed								
No. starting interval	680	603	1032	1,578	2,009	1222	554	2,367
Woman-years	5424	2924	3926	12,444	13,172	8616	2412	48,919
Breast cancer cases								
Observed (O)	3	1	1	19	29	25	9	87
Expected (E)	1.41	1.48	4.17	23.7	35.2	26.1	8.83	100.9
O/E	2.12	0.68	0.24	0.80	0.82	0.96	1.02	0.86
Relative risk[b]	1.17	0.69	1.23	1.46*	1.37*	1.65*	1.59	1.44*
Fitted relative risk[c]	1.00	1.35	1.40	1.41	1.48	1.60	1.58	1.48
Excess risk[b] $\times 10^{-4}$ WY-Gy	0.57	−2.04	2.57	9.74*	10.0*	20.9*	26.2	8.00
Fitted excess risk[c] $\times 10^{-4}$ WY-Gy	0.00	2.11	4.58	8.63	13.8	19.5	23.6	10.7

[a] Number of women contributing WY of observation in these intervals. Variation is due to survival and to the wide range of intervals between exposure and start of follow-up for many individuals. Women with unknown doses excluded.

[b] Based on maximum-likelihood methods to compute adjusted risk estimates of the ratio of O/E values between exposed and nonexposed, adjusting for differences in background rates between subcohorts. Excess risk also derived from this approach.

[c] Based on best-fitting linear dose–response model accounting for age, calendar year, follow-up, and subcohort.

* $P < 0.05$ (one-sided).

patients with breast cancer *(39)*. On the other hand, a similar decrease in RR with time based on incidence data from the atomic bomb survivors study is also suggested *(34)*. The TB patients in our study were followed for more than 50 years, and no significant diminution of breast cancer risk was observed. In fact, on an absolute scale the excess risk increased significantly over time. This suggests, at least for radiogenic breast cancer, that the risk of radiation exposures may last throughout life. Further, it appears that the risk of radiogenic breast cancer over time is proportional to the background cancer incidence rate, and varies in a manner consistent with a constant RR time-response model. This implies that women heavily exposed when young should be monitored carefully in later life when the incidence of breast cancer is especially high.

Age at exposure is perhaps the most important factor that modifies the risk of radiation-induced breast cancer. It appears that risk decreases with increasing age at exposure, and that exposures when young inflict more injury than exposures at older ages. Possibly, the developing breast may be especially susceptible to carcinogens such as ionizing radiation. High risks following exposures during the teenage years have also been observed among atomic bomb survivors *(23)*, Canadian TB fluoroscopy patients *(22, 40)*, patients treated for Hodgkin's disease *(41)*, and women with scoliosis exposed to large numbers of diagnostic X rays (42). Early childhood exposures also carry some risk as seen in studies of atomic bomb survivors *(23)* and children irradiated for thymic enlargement *(43)* and cancer *(44)*. No increase in breast cancer, however, has been reported following fluoroscopic procedures in childhood during heart catheterization *(45)*.

That risk decreases with increasing age at exposure is especially noteworthy when considering mass screening programs of asymptomatic women for the early detection of breast cancer. The natural occurrence of breast cancer increases with age, and women over age 40 are now strongly encouraged to undergo periodic mammographic X-ray examinations *(3)*. As long as there is a benefit from the X-ray screening procedures at these relatively young ages, excessive concern over the possibility of radiation-induced breast cancers in later life is probably not warranted *(46)*. Our study and the similarly large Canadian TB series *(22)* indicate that fractionated exposures to chest fluoroscopy among women over age 40 carry little if any detectable risk. A similar decrease in risk with increasing age is seen among

atomic bomb survivors *(23).* The results of a recent large study of cervical cancer patients who received incidental breast exposures of approximately 30 cGy during radiotherapy also indicate that if women over age 40 are at risk for radiation-induced breast cancer, the risk per unit dose is much lower than seen in studies of younger women exposed to higher doses *(47).*

The time between exposure and appearance of breast cancer appears to be inversely related to age at exposure, i.e.. the latent period is longer in young women than in older women *(48).* Accordingly, the 15-year minimum latent period seen in our study probably reflects the relatively young age of the exposed TB population in comparison with other studies of radiogenic breast cancer reporting increases at earlier times. The fact that radiogenic breast cancer does not occur until later life when the natural occurrence of breast cancer is high also suggests that changes, perhaps promotional or hormonal. are necessary for the prior radiation injury to be expressed as a malignancy. This observation, coupled with the absence of a risk when exposures occur after the menopausal years, support the view that it is the events during the reproductive period in younger women which determine in large part her future risk of breast cancer *(49).*

More dose-response information exists on radiation-induced breast cancer than for any other malignancy. Studies of women exposed to atomic bomb radiation *(23),* to high-dose radiotherapy for mastitis *(24),* or thymic enlargement *(43),* and to chest X-ray fluoroscopy during lung collapse treatments *(9, 22)* all find that a straight line adequately describes the relationship between dose and breast cancer risk. Despite the wide range of different exposure patterns experienced, this similarity in the shape of the dose–response relationship is remarkable *(28, 29).* Our extended series provides additional support to these findings. Quadratic and linear-quadratic curves were rejected as providing less satisfactory fits than a simple linear relationship between radiation dose and breast cancer risk. Further, our excess risk estimates of 61% per Gy and $10.7/10^4$ WY-Gy are generally consistent with those from these other studies on an age-specific basis. Additional and more detailed comparisons will be the basis of a future report.

When evaluating our data several strengths and weaknesses should be considered. The strengths include the large number of incident breast cancer cases observed, the complete and lengthy period of observation, the existence of a nonexposed comparison group, the strong evidence for a dose response. and the consistency with other studies. The major weakness concerns the inherent inaccuracies in breast dosimetry. Although the number of fluoroscopies is known with high accuracy. there are uncertainties associated with the patient orientation and length of time during fluoroscopy. These factors have been considered in detail (14), but nonetheless the radiation risk estimates and the shape of the dose-response relationship would differ if different assumptions had been used. Excluding the pre-1970 follow-up experience of patients in the two new TB cohorts also might have introduced some bias, but we believe this would be small compared to the underascertainment problem of missing perhaps as many as one-third of the incident cases of breast cancer in these early years after hospital discharge. These exclusions did reduce appreciably the number of women under observation shortly after exposure to chest fluoroscopy, and inferences on minimum latent periods had to be based in large part on the earlier TB cohort, which was somewhat smaller and younger. Finally, it is possible that breast cancer might have been underascertainment in the subcohorts 2 and 3 as indicated by lower background rates of breast cancer among the nonexposed compared to those seen in subcohort 1. A principal difference between these subcohorts is that the earlier one derived from a children's hospital, whereas subcohorts 2 and 3 derived from sanatoria for adults. It is unclear whether this age difference would affect background rates. Regardless, since the lower background rates of breast cancer were not correlated with exposure, and radiation risk estimates did not differ between subcohorts, serious bias seems unlikely.

ACKNOWLEDGMENTS

We are indebted to the personnel of the former tuberculosis sanatoria in Massachusetts who willingly allowed us access to their records; to Mr. Daniel Wilson, Dr. Charles Eastlack, and Ms. Carole Prusinowski of Westat, Inc., for providing essential field and data management support: to Ms. Cathy Drzyzgula and Joseph Barker of Information Management Services for computing support: to Glenn Martin of the Health Care Financing Administration for providing assistance in tracing Medicare recipients in Massachusetts: to Dr. Marvin Rosenstein of the Center for Devices and Radiological Health, Food and Drug Administration for providing dosimetry support over the years: to Mrs. Judy Constantian and Mrs. Dorothy Bowen for providing critical tracing support during the early years of the study: to Ms. Maria Klebanoff for manuscript typing: and to Dr. Shields Warren for suggesting the study and supporting it until his death in 1980. This research was partially supported by contracts N01-CP8-5604, N01-CP6-1006, and N01-CP8-1058 with the National Cancer Institute. United States Public Health Service.

RECEIVED: April 11, 1990: ACCEPTED: August 29, 1990

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